Quantitative Ultrasound Measurements of Common Carotid Artery Blood Flow Velocity Patterns in Patients with Coronary Slow Flow

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Öz

Amaç: Koroner yavaş akımlı (CSF) hastalarda karotis akım hızı (CFV) değişkenlerini analiz etmeyi amaçladık.

Yöntem Çalışmaya anjiyografik olarak normal koroner arter yapısına sahip CSF' lu 66 hasta ve normal koroner arter ve normal kan akımına sahip 53 kontrol alındı. Koroner akım, miyokard İnfarktüsü frame Sayımı (cTFC) için düzeltilmiş tromboliz ile ölçümü ile hesaplandı. İntima media kalınlığı (IMT) ve CFV ölçüldü. Brakiyal arter endotel bağımlı dilasyon (EDD) hesaplandı.

Bulgular IMT, pulsatilite indeksi (PI) ve direnç indeksi (RI) CSF grubunda anlamlı derecede yüksek, aksine pik sistolik hız (PSV), uç diyastolik hız (EDV), ortalama hız (MV), çapa bağlı akımda yükselme (FMID), EDD, nitrogliserinle indüklenen dilatasyon (NID) ve hiperemi anlamlı olarak bu grupta düşük izlendi ($p < 0,001$, hepsi için). Spearman korelasyon analizi karotid arter kan akım hızı paternleri ile CSF arasında orta derecede güçlü bir ilişki olduğunu göstermiştir ($p < 0,05$, hepsi için).

Sonuç CSF' lu hastalarda CFV azalmıştır. CSF' da olduğu gibi karotis akış hızındaki azalmanın nedenleri, endotel disfonksiyonu, mikrovasküler direnç ve küçük damar hastalığı olabilir.

Anahtar Kelimeler: koroner yavaş akım, uç diyastolik hız, pik sistolik hız, pulsatilite indeksi, direnç indexi

Abstract

Object We aimed to analyse the carotid flow velocity (CFV) entities of patients with coronary slow flow (CSF).

Methods The study population consisted of 66 patients with angiographically normal coronary arteries and CSF; 53 patients with normal coronary arteries and normal flow. Coronary flow was quantified by corrected Thrombolysis in Myocardial Infarction Frame Count (cTFC). Intima media thickness (IMT) and CFV entities were measured. The brachial artery endothelium dependent dilation (EDD) was calculated.

Results IMT, pulsatility index (PI), and resistive index (RI) were significantly higher; conversely, peak systolic velocity (PSV), end diastolic velocity (EDV), mean velocity (MV), Flow mediated increase in diameter (FMID), EDD, nitroglycerin induced dilation (NID) and hyperaemia were significantly lower in CSF group ($p < 0.001$, for all). Spearman rank correlation analysis showed a moderately strong relationship between carotid artery blood flow velocity patterns and CSF ($p < 0.05$, for all).

Conclusion CFV decreased in patients with CSF. The reasons for the decrease in the carotid flow rate, as in CSF might be endothelial dysfunction, microvascular resistance, and small vessel disease.

Key words: coronary slow flow, end diastolic velocity, peak systolic velocity, pulsatility index, resistive index

Introduction

Coronary slow flow (CSF) is a special disease entity is defined as a normal coronary arteries with delayed filling defect in the distal vasculature[1]. The reported incidence of CSF ranges from 1% to 6% among patients with suspected coronary heart disease[2]. Although several mechanisms have been considered for the etiology of CSF, the underlying pathophysiological mechanisms are not clearly understood[3]. Mechanisms such as endothelial dysfunction, atherosclerosis, impaired microvascular circulation have been shown to have significant correlation with CSF. The corrected Thrombolysis in Myocardial Infarction frame count (CTFC) is an objective method of determining CSF that counts the number of cineangiographic frames of initial contrast opacification of the proximal coronary artery and distal opacification of arterial landmarks . Flow-mediated dilation (FMD) of the brachial artery is an endothelial function marker and determine arterial diameter responses to increased flow. Increased intima media thickness (IMT) and decreased FMD have been shown to be closely related to atherosclerosis . A Doppler ultrasound application is a few steps; For each of them, the examiner must make a choice[10]. The incidence of coronary artery disease and cardiovascular disease mortality are associated with the carotid flow rate[11,12]. We aimed to analyse the carotid flow rate variables of patients with CSF.

Methods

This observational clinical study was conducted between June 2016 and February 2017. The local ethics committee found this study to be appropriate and received written informed consent from all patients in accordance with the Helsinki Declaration.

Study population

The study population involved 66 patients (53 men and 13 women) with angiographically slow flow (normal coronary) in at least one major epicardial coronary artery, and 53 controls (44 men and 9 women) with normal coronary flow (normal coronary). All patients underwent coronary angiography due to typical chest pain or the detection of myocardial ischemia via a treadmill exercise test or myocardial scintigraphy. Exclusion criteria of the study were subjects with known heart failure; coronary artery disease (including spasm, myocardial bridging aneurysms or athero-ectasia); hypertension; diabetes mellitus; valvular heart disease; renal or hepatic dysfunction; peripheral artery disease; stroke; carotid stenosis; and plaque. Blood samples were taken at the time of admission, and transthoracic echocardiography was performed before elective coronary angiography. Angle-corrected flow velocities and waveform parameters were calculated in common carotid arteries (CCAs) by duplex Doppler ultrasonography after coronary angiography.

Determination of TFC and diagnosis of CSF

Selective coronary angiography was performed via the femoral approach using the standard Judkins technique with a rate of 30 frames/s in multiple angulated views (Allura Xper FD10; Philips Healthcare, Best, The Netherlands). Coronary angiograms of all individuals were analyzed by an experienced cardiologist. The left anterior descending (LAD) coronary artery and left circumflex (CX) coronary artery were viewed in a left anterior oblique projection with caudal and cranial angulations. Right coronary artery (RCA) visualization was performed in a left anterior oblique projection with caudal angulations. Iopromide was used as a contrast agent during coronary angiography in all individuals. Patients were evaluated with coronary angiography in terms of CSF presence. Two observers were blinded about the clinical information of the patients and they calculated coronary

flow independently using TFC. The first frame was defined as more than 70% opacification across the proximal coronary artery lumen and indicated forward motion along the artery. The last frame was defined as contrast enhancement of distal coronary landmarks. Normal TFC mean values were 36.2±2.625 frames/s for the LAD, 22.2 ± 4.125 frames/s for the CX, and 20.4 ± 3 frames/s for the RCA within 30 frames/s. LAD frame counts were divided by 1.7 to calculate correct value, as the TFC is often higher for this artery. As a result, the standard CTFC for the LAD was 21.1 ± 1.5 frames/s. All individuals with CTFCs more than 2 standard deviations from the previously reported normal range for a given vessel were determined to have CSF.

Echocardiographic examinations

Echocardiographic examinations were administered by two experienced cardiologists who were blinded to the study data. The measurements were obtained from standard precordial views in the left lateral decubitus position using a Vivid E9 (Bioject Medical Technologies Inc., USA) echocardiography device and were recorded according to the recommendations of the American Society of Echocardiography[13]. All patients underwent standard echocardiographic examinations. The ejection fraction was calculated by using M-mode echocardiography.

Carotid Ultrasonography

CCAs were viewed using a Vivid E9 (Bioject Medical Technologies Inc., USA) with an MLA-15 transducer. All measurements were applied by an experienced radiologist who was blinded to the study data. Each individual was seated in a reclining chair and at a 45 degree angle. The radiologist acquired primary transverse and longitudinal scans of the right CCA at the level of the lower border of the thyroid cartilage, and pulse wave Doppler tracing of the flow via the artery. The peak systolic velocity (PSV), end diastolic velocity (EDV), and mean velocity (MV) were measured. The resistive index (RI) and pulsatility index (PI) were calculated automatically by the software provided with the ultrasound machine. The RI was defined as (PSV – EDV) / PSV and the PI was defined as (PSV – EDV) / MV. Intima-media thickness (IMT) was measured three times each in the right and left CCAs at the thickest point on the far distal wall, approximately 1.5 cm proximal to the flow divider. An IMT > 0.9 mm was accepted as positive.

Brachial arterial reactivity

To measure endothelium dependent and independent dilatation, the ultrasonography was performed as previously described[1] . Purchase of alcoholic or caffeinated drinks was banned 12 hours before the process. Imaging was performed in a dark and silent room at room temperature. All vasoactive drugs were discontinued 24 hours prior to all measurements. After at least 30 min rest, the right brachial artery diameter (intima to intima) was measured three times and the average of these three measurements was recorded as the basal diameter. Arterial diameter above the cuff was imaged and measured. Cuff was inflated to 300 mm Hg for 5 min due to induce reactive hyperaemia; the longitudinal image of the artery was recorded 30 seconds before and 2 minutes after cuff deflation. After 5 minutes, rest images were recorded. Sublingual glyceryl trinitrate (400 g spray) was given, and after 3 minutes the last images of artery was obtained. Endothelium-dependent dilation (EDD) was defined as the percentage change in the brachial artery internal diameter from baseline to hyperemic phase and nitroglycerin induced dilation (NID) defined as dilatation after sublingual nitroglycerin administration respectively. EDD of the brachial artery is an indicator of endothelial function and predicts cardiovascular events[1] . All ultrasound examination were per-

formed after coronary angiography. In general, 10% or more increase in brachial artery diameters measured by the brachial artery FMD method suggests that endothelial functions are preserved[1] .

Study protocol

Information on patients' demographic characteristics, cardiovascular history, and risk factors was obtained from the patients' clinical data. Hyperlipidemia (HL) was defined as low-density lipoprotein (LDL) were greater than 130 mg/dl or triglycerides (TG) were greater than 160 mg/dl or total cholesterol (TC) were greater than 200 mg/dl. Active smokers and patients with smoking histories of at least 1 pack/year until 1 month before study inclusion were considered to have histories of smoking.

Laboratory Parameters

Blood samples were obtained from all patients via antecubital vein puncture immediately before coronary angiography. Blood samples were taken with dipotassium EDTA and evaluated over 30 min. Hematological parameters were measured using an XT-2000i analyzer (Sysmex America Inc., Mundelein, IL, USA). All biochemical parameters were measured using routine laboratory techniques.

Statistical analysis

The SPSS statistical software (SPSS for Windows, version 21.0; SPSS Inc., Chicago, IL, USA) was used for all statistical calculations. The normality of data distribution was analyzed using the Kolmogorov–Smirnov test. Categorical variables are expressed as numbers and proportions, and continuous variables are expressed as means ± standard deviations. Independent-sample Student's t-tests were used for categorical variables, and Mann–Whitney U-tests were employed when the distribution was skewed. The categorical variables between the groups were compared by chi square test. Correlations between baseline biomarkers were assessed with Pearson's and Spearman's correlation coefficients. The statistical significance of the findings was interpreted based on p-values. The level of statistical significance was determined as $p < 0.05$.

Results

The clinical and demographic features of 119 patients are shown in Table 1. As presented in this table, the study population was split into two groups (normal coronary group and CSF group). The study population consisted of 66 patients with CSF (mean age, 54.37 ± 7.01 years) and a control group of 53 patients with normal coronary arteries (mean age, 56.20 ± 6.97 years). Age, gender and left ventricular ejection fraction (LVEF) were similar between groups ($p > 0.05$, for all). The incidence of smoking, hyperlipidemia were significantly higher in the CSF group ($p = 0.043$ and $p = 0.001$, respectively). Values for all blood laboratory parameters were similar between the groups ($p > 0.05$, for all) (Table 1).

The IMT, PI, and RI were significantly higher in the CSF group ($p < 0.001$, for all). In contrast, PSV, EDV, and MV were significantly lower in the CSF group ($p < 0.001$, for all). Brachial vessel diameter did not differ between groups ($p > 0.05$). Flow-mediated increase in diameter and the incidence of EDD, NID and hyperaemia were greater in the control group ($p < 0.001$) (Table 2).

Spearman's analysis of correlation between series for CSF showed strong correlation for the RI ($r = 0,534$, $p < 0.001$) and PI ($r = 0.355$, $p = 0.001$), but inverse correlation for the PSV ($r = -0.619$,

p < 0.001), EDV (r = –0.734, p < 0.001), MV (r = –0.613, p < 0.001), IMT (r = 0.817, p < 0.001), EDD (r= -0.880, p < 0.001), NID (r= -0.837, p < 0.001), hyperaemia (r= -0.782, p= 0.001) and flow-mediated increase in diameter (r= -0.548, p < 0.001) (Table 3). IMT was inversely correlated with FMD (r = -0.491, p < 0.001) (Figure 1). In contrast, PSV and EDV were positively correlated with FMD (r = 0.436, p < 0.001 and r = 0.410, p < 0.001) (Figure 2, Figure 3).

Table 1. Clinical characteristics, laboratory and angiographic findings

Variables	Control group (53)	CSF group (66)	P values
Age, years	56.2±6.9	54.3±7.01	0.160
Gender, male, n, (%)	37	44,5	0.704
Smoking, n, (%)	7 (5.9)	27 (22.7)	0.001*
HL, n, (%)	11 (9.2)	25 (21)	0.043*
LV-EF, (%)	58.1±3.8	58.1±3.2	0.996
Glu (mg/dL)	118.5±47.4	115.4±46.3	0.673
Cre (mg/dL)	0.84±0.12	0.84±0.13	0.853
TC (mg/dl)	188.0±34.8	194.6±49.0	0.410
TG (mg/dl)	183.4±147.6	192.0±122.4	0.731
HDL (mg/dl)	36.9±9.8	38.7±18.2	0.877
LDL (mg/dl)	118.8±29.3	123.3±24.6	0.374
WBC (10^3 × µL)	8.6±3.05	8.3±2.4	0.799
HGB (g/dl)	14.8±1.99	14.9±2.1	0.748
Plt (10^3 × µL	245.0±70.1	240.2±56.3	0.761
TIMI frame count (frame/s)			
CX	24.6±4.4	40.5±8.4	<0.001*
LADc	24.5±5.08	42.3±7.9	
RCA	18.5±3.4	29.9±5.15	
Mean TFC	22.5±4.1	37.6±6.7	

P value<0.05
Cre, creatinine; CX, circumflex artery; Glu, glucose; HGB, hemoglobin; Hl, hyperlipidemia; LAD, left anterior descending; LV-EF, Left ventricular ejection fraction; Plt, platelet; RCA, right coronary artery; TC, total cholesterol; TIMI, Thrombolysis in Myocardial Infarction frame count; TG, triglyceride; WBC, white blood cell

Table 2. Brachial and carotid artery doppler ultrasound measurements

Brachial doppler measurements	Control group (53)	CSF group (66)	P values
Brachial vessel diameter (mm)	3.0±0.12	3.0±0.10	0.240
Flow-mediated increase in diameter (mm)	0.31±0.3	0.26±0.4	< 0.001*
Brachial vascular reactivities			
EDD (%)	10.5±0.7	8.1±0.5	< 0.001*
NID (%)	11.7±0.7	9.7±0.6	
Hyperaemia (%)	469.6±12.5	436.6±13.6	
Carotid doppler measurements			
IMT (mm)	0.71±0.48	1.18±0.16	< 0.001*
PSV (cm/s)	87.4±5.1	79.4±5.1	
EDV (cm/s)	30.9±2.5	24.3±3.4	
MV (cm/s)	64.0±5.1	56.4±4.8	
RI	1.8±0.2	2.3±0.4	
PI	0.88±0.10	0.98±0.14	

*P value<0.05
EDD, endothelium dependent dilation; EDV, end diastolic velocity; IMT, intima-media thickness; LAD, left anterior descending; MV, mean velocity; NID, nitroglycerin-induced dilation; RI, resistive index; PI, pulsatility index; PSV, peac systolic velocity

Table 3. Factors associated with coronary slow flow		
Variables	Correlation coefficient (r)	P value
Age, years	-0.129	0.161
LV-EF, (%)	0.000	0.996
Brachial vessel diameter (mm)	0.108	0.240
Flow-mediated increase in diameter (mm)	-0.548	< 0.001*
EDD (%)	-0.880	< 0.001*
NID (%)	-0.837	< 0.001*
Hyperaemia (%)	-0.782	< 0.001*
IMT (mm)	0.817	< 0.001*
RI	0.534	< 0.001*
PI	0.355	< 0.001*
PSV (m/s)	-0.619	< 0.001*
EDV (m/s)	-0.734	< 0.001*
MV (cm/s)	-0.613	< 0.001*
*P value<0.05		
EDD, endothelium dependent dilation; EDV, end diastolic velocity; IMT, intima-media thickness; LAD, left anterior descending; LV-EF, Left ventricular ejection fraction; MV, mean velocity; NID, nitroglycerin-induced dilation; RI, resistive index; PI, pulsatility index; PSV, peac systolic velocity		

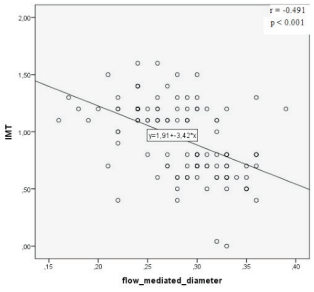

Figure 1. Correlation between intima media thickness and flow mediated increase in diameter

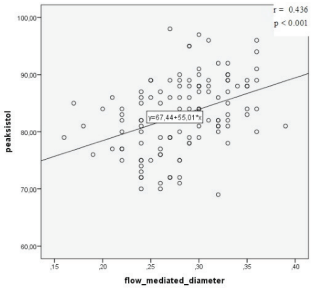

Figure 2. Correlation between peak systolic velocity and flow mediated increase in diameter

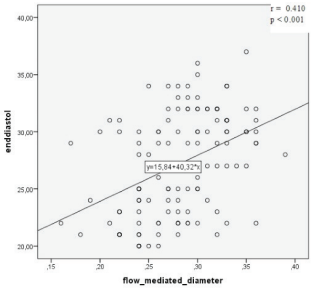

Figure 3. Correlation between end diastolic velocity and flow mediated increase in diameter

Discussion

The present study demonstrated the relationship between carotid artery blood flow velocity patterns with the CSF. To our knowledge, this is the first study to prove an association between carotid artery flow velocity measurements and CSF. In our study, significantly upper carotid IMT measures, significantly impaired FMD, and significantly decreased carotid flow velocity parameters in CSF patients.

Many mechanisms may be responsible for CSF, and the cause has not yet been completely elucidated. The main causes of CSF are endothelial and microvascular dysfunction, abnormal neurohormonal activity, and small vessel disorders[1] . Tambe et al.[1] claimed that CSF is associated with microvascular resistance. Sezgin et al.[1] reported that endothelial dysfunction caused a reduction in NO levels in plasma and flow-mediated vasodilation. These findings reveal functional obstructions in the microvascular system related to these mechanisms.

Based on the classic concept of arterial hemodinamics, blood flow and BP mainly control the luminal radius and wall thickness. Assuming that; collagen and elastin are necessarily structural contri-

butions to increased wall thickness[20]. Arterial endothelial dysfunction appears an early stage in the atherosclerotic process, and is largely due to the impaired bioavailability of NO[21]. Early atherosclerosis can be detected by measuring carotid IMT using Doppler ultrasonography. Suwaidi et al.[22] reported that without obstructive lesions coronary endothelial dysfunction significantly associated with increased cardiovascular disease. Schachinger et al.[23] claimed that abnormal vasodilation to both endothelium-dependent and -independent agonists predicted cardiovascular events in 147 patients during a 7.7-year.

Brachial artery FMD may be a benificial facility for determining coronary artery disease. It may be advisable to patients with reduced FMD to initiate life style changes and other preventions. Lower FMD was determined in patients with mild coronary artery disease, indicating that FMD is useful for predicting initial stages of CAD[2] . FMD was frequently related with enhanced IMT over a 6-year period. This outcome implicits that endothelial function as a causal determinant of atherogenesis[2] . In contrast, Enderle and cols.[2] reported that no relationship between FMD and the severity of coronary artery disease. Hunink et al.[2] reported that lower PSV in the CCA corresponds to higher-grade stenosis in the internal carotid artery (ICA). In contrast, in our study we observed no evidence of plaque or stenosis, except for increased IMT and lower PSV and EDV values, in the CCAs of patients with CSF. In addition, individuals had normal LVEFs. Other studies have shown that abnormalities of the carotid artery lumen and wall are related strongly to cardiovascular risk factors[2] ,[2] . Our data demonstrated that the CCA is easier to image than are the ICA and external carotid artery. Measurements obtained from the CCA are thus less variable and more reliable than those obtained from the ICA and external carotid artery (ECA)[30]. Surprisingly, the CCA flow velocity and diameter appear to be related with ischemic stroke independently of carotid atherosclerosis and cardiovascular disease risk factors[31]. Fukuhara et al.[32] considered that the intracranial arterial circulation in patients with atherosclerosis is increased due to lumen narrowing and enhanced elastic modulus (reduced arterial wall expandability), but magnetic resonance angiograms probably are not useful to show these changes in most patients. Such an increase in downstream circulating resistance causes a decrease in volume flow (unless BP increases) and a partial decrease in flow rate (unless the diameter decreases). The outcome of a significant positive relation between fractional shortening and PSV indicates that carotid flow rate is sensitive to cardiac hemodynamic changes. Similarly, there is a synergistic relationship between flow velocity in the middle cerebral artery and cardiac index was reported in normotensive patients. In our study, the patients were normotensive and had no heart failure. Owolabi et al.[33] showed that diameter and blood flow velocities showed weak correlation for the carotid arteries, but strong correlation for the vertebral arteries of stroke patients, even after controlling for age, sex, and BP. Variations in carotid flow rates after exposure to external variables (physical activity, temperature, food intake, light, and noise) can be seen[3] . Ray-Caudhuri et al.[3] have shown that the PI is a semiquantitative index which symbolizes blood flow impedance downstream of the point of sampling and ensures a measure of arteriolar tone[3] . The hemodynamic RI of the ICA correlates with the degree of arteriosclerosis[3] .

Study Limitations

First, this work was based on limited numbers of patients and controls. Second, we did not conduct long-term follow-up. Third, Pulse wave velocity (PWV) has a determinative role for left ventricular function and coronary blood flow, can affect carotid blood flow velocity, and should be measured to clarify arterial stiffness. The lack of PWV calculation was a limitation of this study. Finally, varia-

tions in carotid flow rates after exposure to external variables (physical activity, temperature, food intake, light, and noise) can be seen. Further studies are required before these findings are applied in clinical practice.

Conclusion

This report is the first to focus on the relationship between measurements of carotid blood flow velocity patterns with CSF. The reasons for the decrease in the carotid flow rate, as in CSF might be endothelial dysfunction, microvascular resistance, and small vessel disease.

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Conflict of interest

No conflict of interest was declared by the authors.

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